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Dietary patterns and respiratory health in adults from nine European countries – evidence from the GA²LEN study

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Short Running Head: Dietary intake and respiratory health in European adults

Abbreviations:

PCA: Principal Component Analysis

meta-PCA: meta-analytic approach to PCA

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

LLN: lower limit of normal

COPD: chronic obstructive pulmonary disease

FFQ: food frequency questionnaire

GA²LEN: Global Asthma and Allergy Network of Excellence

SPT: skin prick test

SOB: attack of shortness of breath

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IgE: Immunoglobulin E

PUFAs: polyunsaturated fatty acids

BMI: body mass index

RR: Relative Risk

CI: Confidence Intervals

MD: mean difference

ABSTRACT

Background: Dietary patterns defined using Principal Component Analysis (PCA) offer an alternative to the analysis of individual foods and nutrients and have been linked with asthma and allergic disease. However, results have not been reproducible in different settings.

Objective: To identify dietary patterns common to different European countries and examine their associations with asthma and allergic symptoms.

Methods: In sixteen study centres in nine European countries, 3206 individuals aged 15-77 years completed a common, internationally validated, Food Frequency Questionnaire and a respiratory symptoms questionnaire. The outcomes of interest were current asthma, asthma symptoms score (derived based on responses to 5 asthma symptom-related questions), atopy (positive skin prick test). Spirometry was used to estimate forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), the FEV₁/FVC, spirometric restriction (FVC below the lower limit of normal (<LLN)) and FEV₁/FVC < LLN. A novel meta-analytic approach was used to identify dietary patterns using PCA and to examine associations with asthma and allergic symptoms.

Results: Two dietary patterns emerged, generally correlating with the same foods in different countries: one associated with intake of animal proteins and carbohydrates; the other with fruit and vegetables. There was evidence that the former pattern was associated with a higher asthma score (RR 1.63, 95% CI: 1.33-2.01), current asthma (RR 2.03, 95% CI: 1.52-2.71), wheeze (RR 1.84, 95%CI: 1.30-2.60), atopic status (RR 1.68, 95%CI: 1.16-2.44) and with decreased lung function, including an FVC <LLN (RR 4.57, 95% CI: 2.27-9.21).

Conclusions & Clinical Relevance: Our findings suggest an increase in sensitisation to common allergens, an increase in asthma symptoms and a reduction in lung function in those eating a diet rich in animal proteins and carbohydrates. We found little evidence of an association between these outcomes and eating a diet rich in fruits and vegetables.

Keywords: principal components analysis, dietary patterns, nutritional epidemiology, asthma, meta-regression

INTRODUCTION

There is accumulating evidence from observational studies that high intakes of fruit and vegetables have a protective effect in children and adults with asthma.¹ Additionally, asthma has been associated with low intakes of dietary antioxidants and particularly with vitamins C, D and E and selenium.²⁻⁴ However, trials of supplementation have been unsuccessful and have contradicted the findings from observational studies.⁵⁻⁷ This may be because apparent effects in the observational studies were confounded by lifestyle factors or by other dietary components.^{8,9}

In the last decade, the use of Principal Component Analysis (PCA) has offered an alternative to analysing dietary exposures as single foods or nutrients, by empirically identifying consistent dietary patterns. Observational studies in adults from Europe have shown a positive association between dietary patterns that reflect a more 'Western diet' and asthma risk,¹⁰⁻¹³ and have been associated with lower ventilatory function.¹⁴ On the other hand, having a 'prudent' pattern, usually characterised by fruit and vegetable intake, has been associated with lower risk of chronic obstructive pulmonary disease (COPD)^{15,16} and better ventilatory function.^{13,14} However, other population-based studies have not confirmed these associations when linking PCA derived dietary patterns to asthma,¹⁷ ventilatory function,¹⁸ or allergy-related outcomes.^{17,19} A possible reason for the contradictory findings is that results from dietary patterns derived with the use of PCA have not always been reproducible across different settings.²⁰

In order to address this limitation of PCA we used a novel approach for the analysis of food frequency questionnaire (FFQ) data across different countries; a meta-analytic approach to PCA (meta-PCA).¹⁹ Our aim is to explore associations between dietary intake and respiratory and allergic symptoms in European populations participating in the Global Asthma and Allergy Network of Excellence (GA²LEN) study.

METHODS

Study design and population

GA²LEN was a European Union funded network of excellence which coordinated a study of genetic and environmental risk factors for allergy and asthma in adult and adolescent populations across 18 participating centres in 11 European countries. In brief, the GA²LEN follow up survey is a cross-

sectional study amongst those previously contacted in baseline postal surveys of representative adult populations who were willing to be contacted again. Three groups of cases (those with asthma, those with sinusitis, and those with both asthma and sinusitis) and one group of controls (those with neither asthma nor sinusitis) were drawn from the postal survey sample and invited for follow-up. Administered questionnaires were used to obtain information on age, gender, smoking and various environmental factors and the presence of symptoms of asthma, chronic rhino-sinusitis and allergic rhinitis. As part of the GA²LEN Follow-up Survey, we established the GA²LEN Dietary Study, where dietary intake was enquired using a self-completed FFQ ('Dietary intake in adults from the GA²LEN Follow-up Survey ClinicalTrials.gov Identifier: NCT03251157). Clinical assessment was also done, and included measurement of height, weight, allergen skin prick test (SPT), blood samples for total and specific Immunoglobulin E (IgE) and lung function. Detailed description of the study is provided elsewhere.²¹

Respiratory and allergic outcomes

A continuous measure of asthma symptoms (asthma score) was derived.²² It is the sum of positive responses to questions regarding the following symptoms in the last 12 months: wheeze with breathlessness, chest tightness, attack of shortness of breath (SOB) coming on at rest, SOB after exercise, and being woken by SOB. The score ranged from 0 (no symptoms) to 5 (having all the symptoms enquired). Asthma was also defined as present in those who had answered yes to having a diagnosis of asthma and either wheezing, waking up with chest tightness, waking up with shortness of breath, or waking at night with an attack of coughing in the previous 12 months. Other respiratory symptoms included allergic rhinitis, which was defined as a positive response to the question "Do you have any nasal allergies including hay fever?" and eczema was defined as a positive response to the question "Did you ever have eczema or any kind of skin allergy?"

Skin prick tests (SPTs) to grass pollen, grass mix, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cockroach (*Blatella*), olive, *Alternaria*, dog, *Artemisia*, birch, cat and *Parietaria* were conducted. All tests with an average diameter ≥ 3 mm greater than control were taken to be positive (i.e. histamine ≥ 3 mm and negative control < 3 mm). Atopy was defined as any positive response to any of the allergens tested.

Spirometric lung function (Forced Expiratory Volume in one second (FEV₁), and Forced Vital Capacity (FVC)) were measured pre- and post- administration of bronchodilator (salbutamol 200 mg).

Spirometric restriction was defined by an FVC below the lower limit of normal ($< LLN$), and chronic obstruction by an FEV₁/FVC $< LLN$, defined according to the National Health and Nutrition Examination Survey (NHANES) III norms for Caucasians. All spirometries were checked centrally for quality. Only spirometry that met the ERS/ATS criteria was accepted.²³

In all centres permission to conduct this study was obtained from appropriate local ethics committees, and all participants signed a written consent form after being fully informed about the study.

Food Frequency Questionnaire (FFQ)

One GA²LEN survey objective was to assess dietary intake across European countries using a single and standardised instrument that is common to all participant countries. The questionnaire included a set of 32 food sections and 239 food items. The FFQ sections were designed following the recommendations by the EFCOSUM Group,²⁴ which facilitate international comparisons of dietary intake. It also included several staple foods to capture locally representative dietary intake.

The FFQ enquired about intake of foods consumed over a period of 12 months to capture dietary habits during season. Participants reported how often they had consumed the foods over the previous month, using eight predefined options (rarely or never, 1-3 times per month, once, 2-4, or 5-6 times per week, once, 2-3 times per day). Standard food portion sizes were used to quantify the intake following the recommendations from the UK's Food Standards Agency. We estimated weekly intake (g) of foods and food groups by multiplying frequency of consumption by the weight of standard portion sizes. Macronutrient intakes and total energy intake (TEI) were derived using the latest available edition of McCance & Widdowson's Food Composition Tables.²⁵

Respondents sometimes left individual items blank on the FFQs. This was assumed to denote zero intakes of these foods unless more than 20% of items were blank, in which case the FFQ was considered incomplete, and the subject was excluded from analyses. Participants were also excluded if they had extreme values of total energy intake, which might suggest an unrealistic response. We calculated the expected basal metabolic rate (BMR) with the given age, weight, and sex, and excluded subjects with a ratio of energy intake to expected BMR that was either below the 0.05th sample centile or above the 99.5th sample centile for their country.

We have included in our analysis only food items which were consumed at least 1-3 times per week by more than 5% of the individuals in our final sample.

The GA²LEN FFQ was validated in five EU countries, namely Finland, Portugal, Germany, Poland, and Greece) and demonstrated to be a good tool to assess mid-term intake of foods, specifically essential polyunsaturated fatty acids (PUFAs).²¹ The instrument has also been demonstrated to be an accurate tool to assess dietary sources of flavonoids.²⁶

Statistical analyses

Dietary pattern analyses with the use of meta-PCA

We derived dietary patterns using a meta-analytic method proposed by Hedges & Olkin.²⁷ This analysis was restricted to control participants in order to reflect diet in a healthy population. In each country we evaluated a Pearson product moment correlation, r , for each pair of food items. Each correlation coefficient was then transformed using a Fisher transformation

$$z = 0.5 \log \left(\frac{1 + r}{1 - r} \right)$$

to give it an approximately normal distribution with variance $1/(n-3)$, where n is the sample size for the country in question. For each pair of food items, a weighted average of these z -values over all countries was calculated, using the inverse variance ($n - 3$) as a weighting, and an inverse Fisher transformation was then applied to give a pooled correlation coefficient. A more detailed description of the method is provided in the technical note of the online supplemental material. Finally, PCA was applied to the matrix of pooled correlation coefficients, giving us dietary pattern scores (linear combinations of standardised food intakes) which could be used in all countries. A varimax rotation was applied to improve the interpretability of the patterns obtained, and the number of patterns extracted was chosen based on interpretability and an examination of the scree plot. This meta-analytic approach to PCA (meta-PCA) has previously been applied in the field of psychiatry^{28,29} and we have used it previously in dietary analysis.¹⁹

Asthma and allergic symptoms

Within each country we used Poisson regression models with a robust error variance and linear regression models to investigate associations between dietary patterns (categorised in quintile groups) and respiratory and allergic outcomes. Regression results were pooled across countries using random effects meta-analysis, and heterogeneity was summarised using the I^2 statistic.³⁰

Confounders

All analyses were adjusted for the following potential confounders identified *a priori*: age, sex, smoking status (never, ex-smoker, current), body mass index (BMI), age at completion of full time education, occupation, use of nutritional supplements, dietary patterns and total energy intake (TEI).

Further adjustment for weight and height were included when association between dietary intake and lung function measurements were examined. Sampling probability weights for each subject in each subset of the survey data were computed by dividing the frequency of the subject's centre and case status in the postal survey by the frequency of this centre and case status in the analysis dataset.

Statistical analyses were conducted using STATA 14.1 (Stata Corporation, College Station, Texas USA).

RESULTS

Centres in Palermo (Italy), and Skopje (Macedonia) were excluded because of the small number of cases and additionally small number of individuals who completed the FFQ (n=32 and n=26, respectively). We analysed the two German centres (Brandenburg, Duisburg) as if they were from different countries because of socio-economic and demographic differences between their

populations. Our final sample included 3206 individuals living in 16 centres in 9 countries with full data on FFQ data and confounders. 43 food items were excluded from our analysis due to infrequent consumption, leaving 196 out of the original 239 items. In total, 120 subjects were excluded from the study due to incomplete or implausible total energy intake. We compared the characteristics of those included (n=3,206) and excluded (n=120) from the study, and both samples were very similar in terms of age, sex, BMI, education, employment and smoking. Further descriptive data on health outcomes and confounders are presented in Table 1.

Dietary patterns identified with the use of meta-PCA

We extracted two dietary patterns, which explained 16.8% of the variance in the original 196 items. A component score was created for each individual for each of the principal components identified. Table S1 (see online supplement) presents individual food items that correlated ≥ 0.3 or ≤ -0.3 with the varimax rotated dietary patterns (principal components) in more than five different countries. According to Table S1 (see online supplement), in more than five countries the first pattern was characterized by high consumption of fruits and vegetables and the second one was closely associated with intakes of animal proteins and carbohydrates, and thus patterns were labelled accordingly.

Asthma and allergic symptoms

There was evidence of an association of the animal proteins and carbohydrates pattern with asthma score (RR 1.63 per quintile, 95% CI: 1.33-2.01), self-reported asthma in the last 12 months (RR 2.03 per quintile, 95% CI: 1.52-2.71), doctor diagnosed asthma (RR 1.71 per quintile, 95% CI: 1.22-2.38), ever had asthma (RR 1.61 per quintile, 95% CI: 1.17-2.22), wheeze in the last 12 months (RR 1.84 per

quintile, 95%CI: 1.30-2.60), positive skin prick test to house dust mite (RR 1.39 per quintile; 95% CI: 1.00-2.01), and positive skin prick test to at least one of the 11 allergens (RR 1.68 per quintile; 95% CI: 1.16-2.44) (Table 2). For lung function, significant associations were seen suggesting increases in risk of FVC < LLN and decreases of pre-and post-bronchodilator mean differences of FEV₁ and FVC, in association with the animal proteins and carbohydrates pattern (Table 3). This was not the case for the FEV₁/FVC ratio. There was no evidence of heterogeneity in the statistically significant associations between the selected respiratory and allergic outcomes with the animal proteins and carbohydrates pattern (p values for heterogeneity were above 0.1).

There was no evidence that a fruit and vegetables pattern was associated with any of the respiratory or allergic outcomes (Table 2). There was no evidence of heterogeneity in the effects associated with an animal protein and carbohydrate dietary pattern, which were consistent across countries. However, there was evidence of heterogeneity in the association of asthma score with the fruit and vegetables pattern ($I^2=50.5\%$; $P=0.033$) and, when countries were analysed separately, increased fruit and vegetables pattern intake was associated with a decreased asthma score in Poland (RR per quintile 0.50; 95% CI 0.27, 0.94) and an increased score in Belgium (RR per quintile 1.97; 95% CI 1.02, 3.78) (Figure 1). There was also evidence of heterogeneity in the associations of FVC and other lung function measures with the fruit and vegetables dietary pattern (Table 3).

DISCUSSION

This multi-centre study found cross-sectional associations between asthma, wheeze and allergic sensitization and a pattern of dietary intake rich in animal proteins and carbohydrates. This pattern was also associated with small decrements of pre-and post-bronchodilator FEV₁ and FVC. There was no strong evidence that a fruit and vegetables pattern was associated with lung function outcomes.

Our findings of an association of animal proteins and carbohydrates pattern with asthma –related symptoms, but not with rhinitis, might suggest that the mechanisms of action might differ across allergic diseases. Our findings are consistent with previous observational studies of 156,035 adult Australian men and women where a meats/cheese dietary pattern was positively associated with asthma (OR 1.18; 95% CI: 1.08 - 1.28), of 54,672 French women¹⁶ where a Western pattern was associated with an increased risk of reporting frequent asthma attacks (OR 1.79; 95% CI: 1.11–3.73), and the Manchester Asthma and Allergy Study³¹ where a high adherence to a Western diet pattern was significantly associated with doctor-diagnosed asthma and current asthma at age 8 years (OR 2.19; 95% CI: 1.20-4.01; RR 2.59; 95% CI: 1.15-5.81 respectively) and current asthma at age 11 years (OR 2.20; 95% CI: 1.07-4.51),

Lack of associations between our fruit and vegetables pattern and asthma and related allergic symptoms were consistent with other observational studies of 54,672 French women,³² 52,325 male and female adult Chinese Singaporeans³³ and 1453 adults living in Greenwich.¹⁷ Furthermore, our results were consistent with the results of 12008 pregnant women in the Avon Longitudinal Study of Parents and Children³⁴ where no associations were observed between a “health conscious” (similar to our fruit and vegetables) pattern and asthma, atopy or eczema.

Diet is strongly socially, environmentally and culturally patterned with specificities between countries and social groups.³⁵ Heterogeneity in multi-centre studies as observed for the “fruit and vegetable” pattern in Figure 1 could suggest alternative explanations for apparent effects of diet observed in single centers, such as uncontrolled confounding, and would make us cautious about inferring causation and of progressing to a trial.³⁶ From a methodological point of view, it is possible that some of the heterogeneity observed reflects the wider range of foods included in this category (over 50 fruits and vegetables, whilst there were less than 30 sources of animal proteins).

In contrast, it is notable that the associations of the animal proteins and carbohydrates dietary patterns with respiratory and allergic symptoms are very consistent between places with a high degree of homogeneity in the effect estimates (Table 2 and the right hand side of Figure 1).

Our study has several methodological advantages. The analyses we used gives us common dietary patterns (weighted sums of standardised food intakes) that we can investigate at every centre. A meta-analytic approach to deriving dietary patterns across a number of centres has been investigated once before in nutritional epidemiology¹⁹ but has not otherwise been exploited in this setting. This is partly because FFQ are often specific to a site, making it difficult to pool data. Our study has the advantage of using data from an FFQ that allowed directly comparable data to be collected in different countries. We have shown that the method can be successful in identifying common dietary patterns, as well as providing evidence on the heterogeneity in the effects associated with those patterns. However, given the observational nature of the study, we cannot exclude the possibility of residual confounding.

In conclusion, using meta-PCA, we have demonstrated a consistent association across different countries between a diet with a high intake of animal proteins and carbohydrates and respiratory and allergic outcomes and lung function.

Conflict of Interest (COI) Statement: None

Authors' contributions: IB, VGL, RH and PGB conceived the hypothesis for this analysis. IB wrote the first draft of manuscript. VGL designed the GA²LEN FFQ which was used to collect data on dietary intake in the GA²LEN participants. VGL led the international validation of the GA²LEN FFQ. IB and RH conducted with statistical analyses, with input from VGL and PGB. All co-authors listed in the manuscript contributed to and approved the final version of the manuscript and led the research efforts to collect the data in their participant centres. All authors read and approved the final manuscript.

Consent for publication: All co-authors have read and approved the final version of the manuscript and gave their consent to publish it. Ethics approval and consent to participate. The GA²LEN Survey was approved by the UK's National Research Ethics Service (NRES) No 07/H0604/121. In addition, all participant centres were granted ethical approval to take part in the GA²LEN Follow-up survey, from which this analysis was done. Belgium: Committee for Medical Ethics, University of Ghent. Denmark: Den Videnskabsetiske Komite for Region Syddanmark. Finland: Helsingin Ja Uudenmaan Saira Anhoitopiirin Kuntayhtyma, Eetiset toimukunnat. Germany (both centres): Commission of Ethic, Faculty of Medicine, Heirich Heine Universitat Dusseldorf. Poland: Katowice: Biotethics Commision University of Katowice; Krakow (Commision of Bioethics University of Jagiellonskiego; Lodz (Committee of Bioethics University of Lodz. Portugal: Commission of Ethics for Health, Hospital of the University of Coimbra. Sweden (Joint ethical approval for all four participant centres) Karolinska Institute Ethics Committee. The Netherlands: Medical Ethics Committee, Academic Medical Centre, University of Amsterdam.

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TABLES AND FIGURES

TABLE 1. General characteristics of the study population [#] (based on individuals with complete data on dietary exposures and asthma score)

Variables	Countries					
	Denmark	Finland	Sweden	United Kingdom	Germany	Germany
	Odense (359)	Helsinki (160)	Total (1,261)	Total (173)	(Duisburg) (200)	Brandenburg (178)
Asthma score; N (%)						
0	145(40.4)	96 (59.6)	583 (46.2)	66 (38.2)	74 (37.0)	87 (48.8)
1	85 (23.7)	31 (19.3)	276 (21.9)	37 (21.4)	62 (31.0)	45 (25.2)
2	50 (13.9)	15(9.3)	195 (15.5)	22 (12.7)	26 (13.0)	21 (11.8)
3	47 (13.1)	10 (6.2)	114 (9.0)	17 (11.5)	18 (9.0)	17 (9.5)
4	24 (6.7)	7 (4.4)	61 (4.8)	26 (15.0)	10 (5.0)	6 (3.3)
5	8 (2.2)	2 (1.2)	33 (2.6)	5 (2.9)	10 (5.0)	2 (1.2)
Age, years; mean (SD)	48.1 (14.5)	46.8 (15.1)	45.7 (15.1)	51.6 (13.2)	49.0 (15.7)	49.8 (15.3)
Males, n (%)	162 (45.1)	62 (38.8)	556 (44.1)	70 (40.5)	85(42.7)	67 (37.6)
BMI (m ² /kg)	27.4 (14.8)	26.5 (4.6)	25.9 (7.2)	27.1 (5.6)	27.2 (5.1)	26.7 (4.8)
Age at completing full-time education; years (SD)	23.4 (5.5)	23.5 (5.5)	24.5 (7.7)	18.1 (3.6)	20.2 (4.1)	20.7 (4.7)
Employment status						
Employed	188 (52.7)	94 (58.9)	737 (58.5)	85 (49.7)	102(51.2)	94 (52.8)
Retired	82 (23.0)	32 (20.0)	199 (15.8)	39 (22.8)	44 (22.1)	44 (24.7)

Unemployed	11 (3.1)	3 (1.9)	38 (3.0)	4 (2.3)	7 (3.5)	5 (2.8)
Other	76 (21.5)	31 (19.4)	286 (22.7)	43 (25.1)	47 (23.8)	35(19.7)
Smoking						
Never smokers	155 (43.4)	83 (51.9)	672 (53.3)	77 (44.5)	92 (46.0)	91 (51.1)
Ex-smokers	102 (28.6)	37 (23.1)	428 (33.9)	70 (40.5)	75 (37.5)	56 (31.4)
Current smokers	100 (28.0)	40 (25.0)	162 (12.8)	26 (15.0)	33 (16.5)	31 (17.4)
Total Energy Intake (TEI)	2,577 (761)	3,197 (1,140)	3,110 (978)	2,833 (889.6)	2,906 (1,106)	2,734 987)
Use of nutritional supplements, n (%)	143 (40.4)	70 (43.5)	325 (26.0)	58 (33.7)	53 (26.6)	49 (27.5)
% people eating fruits (all types) ≥5 times/week	202 (56.4)	93 (57.1)	717 (56.0)	101 (57.7)	54 (48.2)	60 (54.5)
% people eating total vegetables (all types) ≥5 times/week	224 (62.4)	128 (78.5)	906 (70.7)	92 (52.6)	104 (55.7)	90 (57.8)

TABLE 1. (continued) General characteristics of the study population

Variables	Countries				
	Portugal	Belgium	Poland	The Netherlands	Total
	Coimbra (270)	Ghent (148)	Total (244)	Amsterdam (215)	3,206
Asthma score					
0	109 (41.0)	57 (38.5)	78 (32.0)	100 (41.0)	1,395 (43.5)
1	49 (18.4)	34 (23.0)	73 (29.9)	40 (18.6)	732 (22.8)
2	41 (15.4)	22 (14.9)	34 (13.9)	37 (17.2)	463 (14.4)
3	27 910.2)	17 (11.5)	28 (11.5)	23 (10.7)	318 (9.9)
4	23 (8.7)	12 (8.1)	17 (7.0)	12 (5.6)	198 (6.2)
5	20 (6.4)	6 (4.1)	14 (5.7)	3 (1.4)	100 (3.1)
Age, years; mean (SD)	47.1 (15.0)	45.7 (15.1)	49.7 (15.7)	52.6 (13.9)	47.6 (15.1)
Males, n (%)	93 (35.0)	71 (48.0)	104 (42.6)	111 (51.6)	1,381 (43.1)
BMI, m ² /kg (SD)	25.9 (5.1)	24.9 (4.4)	27.4 (5.2)	25.7 (3.7)	26.3 (5.2)
Age at completing full-time education ; years (SD)	20.1 (4.6)	20.6 (6.6)	20.4 (3.4)	20.2 (4.6)	22.4 (6.6)
Employment status					

Employed	140 (52.6)	75 (51.0)	89 (38.0)	103 (47.9)	1,707 (53.6)
Retired	56 (26.5)	26 (17.7)	86 (36.8)	56 (21.1)	664 (20.8)
Unemployed	11 (4.1)	3 (2.0)	12 (5.1)	5 (2.3)	99 (3.1)
Other	59 (22.2)	30 (22.4)	47 (20.0)	51 (23.7)	717 (22.5)
Smoking					
Never smokers	172 (64.7)	75 (50.7)	111 (45.7)	84 (39.1)	1,612 (50.4)
Ex-smokers	56 (21.1)	45 (30.4)	78 (32.1)	88 (40.9)	1,035 (32.2)
Current smokers	38 (14.3)	28 (18.9)	54 (22.2)	43 (20.0)	555 (17.3)
Total Energy Intake (TEI); mean (SD)	3,195 (1,296)	2,937 (885)	3,211 (1,661)	2,817 (827)	2,993 (1,072)
Use of nutritional supplements, n (%)	16 (6.0)	50 (33.8)	53 (22.0)	88 (41.0)	905 (28.4)
% people eating fruits (all types) ≥5 times/week	189 (70.8)	80 (54.1)	158 (64.0)	114 (52.3)	1,867 (57.6)
% people eating total vegetables (all types) ≥5 times/week	206 (77.2)	77 (52.0)	182 (73.7)	78 (35.8)	2,087 (64.4)

TABLE 2. Associations of selected respiratory and allergic outcomes in relation to dietary patterns adjusted for potential confounders*. Results of meta-analyses of the effect of principal component scores on respiratory and allergic outcomes. Mean difference, Relative Risks (RRs) and 95 % confidence intervals (95% CI) represent increase in risk per quintile of dietary pattern scores. N=3206.

	“Fruit and Vegetables diet”					“Animal proteins and Carbohydrates diet”				
	Mean difference*	95%CI	p-value	i-square (%)	p-value for heterogeneity	Mean difference*	95%CI	p-value	i-square (%)	p-value for heterogeneity
Total IgE (kU/L) †	0.19	-0.09,0.48	0.186	23.1	0.231	0.21	-0.06,0.48	0.131	0	0.737
Questionnaire variables	RR*					RR*				
Asthma score	1.18	0.88,1.57	0.266	50.5	0.033	1.63	1.33,2.01	<0.001	0	0.899
Self-reported asthma in the last 12 months	0.99	0.75,1.30	0.925	0	0.529	2.03	1.52,2.71	<0.001	0	0.462
Doctor diagnosed asthma	0.99	0.67,1.47	0.963	35.4	0.124	1.71	1.22,2.38	<0.001	0	0.713
Ever had asthma	1.03	0.75,1.41	0.844	7.6	0.372	1.61	1.17,2.22	<0.001	0	0.719
Wheeze in the last 12 months	1.1	0.82,1.47	0.538	27.5	0.19	1.84	1.30,2.60	<0.001	32.4	0.149
Eczema in the last 12 months	1.02	0.86,1.22	0.789	18.3	0.274	1.1	0.92,1.32	0.308	15.4	0.301
Allergic rhinitis	0.85	0.61,1.18	0.329	52	0.027	1.12	0.85,1.47	0.423	19.6	0.262
Positive Skin prick tests										
Any of 11 inhalant and food allergens†	0.97	0.78,1.20	0.779	29.5	0.173	1.68	1.16,2.44	0.006	0	0.947

House dust mite (HDM)	1.08	0.76,1.52	0.673	16.2	0.294	1.39	1.00,2.01	0.051	0	0.768
Cat dander	1.29	0.82,2.01	0.266	37.6	0.108	1.5	0.88,2.57	0.137	47.5	0.046
Cockroach	1.2	0.77,1.85	0.427	34.4	0.132	1.05	0.57,1.93	0.873	56.7	0.013
Grass mix	0.93	0.64,1.34	0.69	38.4	0.102	1.2	0.83,1.73	0.337	33.0	0.144
Rye Grass	1.02	0.76,1.37	0.902	11.8	0.333	1.07	0.78,1.45	0.681	7.9	0.369

*Adjusted for age, sex, smoking status (never, ex-smoker, current), body mass index, age at completion of full time education, occupation, use of nutritional supplements and total energy intake (TEI).

TABLE 3. Associations of selected lung function outcomes in relation to dietary patterns adjusted for potential confounders*. Results of meta-analyses of the effect of principal component scores on respiratory and allergic outcomes. Mean difference, Relative Risks (RRs) and 95 % confidence intervals (95% CI) represent increase in risk per quintile of dietary pattern scores. N=3206.

Ventilatory Function (post-bronchodilator measures)	“Fruit and Vegetables diet”					“Animal proteins and Carbohydrates diet”				
	RR**	95%CI	p-value	I-square (%)	p-value of heterogeneity	RR**	95%CI	p-value	i-square (%)	p-value of heterogeneity
FVC below the limit of normal	0.69	0.27,1.70	0.421	69.3	0.001	4.58	2.28,9.22	0.001	50.9	0.031
FEV1/ FVC below the limit of normal	0.47	0.10,2.26	0.352	79.7%	<0.001	1.63	0.81,3.28	0.163	8.0%	0.447
	Mean difference**	95%CI	p-value	I-square (%)	p-value of heterogeneity	Mean difference**	95%CI	p-value	i-square (%)	p-value of heterogeneity
Spirometry										
log (FEV1 pre bronchodilator (L))	0.04	-0.01,0.08	0.112	53.5	0.022	-0.07	-0.11,-0.03	<0.001	12.4	0.329

log (FEV1 post bronchodilator (L))	0.04	-0.01,0.08	0.114	61.6	0.005	-0.06	-0.09,-0.03	<0.001	0	0.471
log (FVC pre bronchodilator (L))	0.01	-0.03,0.05	0.551	53.7	0.021	-0.06	-0.08,-0.03	<0.001	0	0.857
log (FVC post bronchodilator (L))	0.02	-0.03,0.07	0.408	68.9	<0.001	-0.06	-0.08,-0.03	<0.001	0	0.989
FEV1/FVC ratio pre bronchodilator	0.02	0.00,0.03	0.056	0	0.746	-0.01	-0.03,0.01	0.343	13.5	0.318
FEV1/FVC ratio post bronchodilator	0.01	-0.01,0.04	0.217	46.4	0.052	-0.01	-0.03,0.01	0.550	36.1	0.119

* Adjusted for age, weight, height, sex, smoking status (never, ex-smoker, current), body mass index, age at completion of full time education, occupation, use of nutritional supplements and total energy intake (TEI)

FIGURE 1. . Associations between asthma score and “Fruit and Vegetables” and “Animal proteins and Carbohydrates” pattern across 9 countries: results of meta-analyses of the association of

